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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,913	12/22/1998	RODERICK L. HALL	98.736	2461

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1652	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/218,913	Applicant(s) Hall et al.
	Examiner Nashaat T. Nashed	Art Unit 1652

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 22, 1998* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above, claim(s) *11, 12, 14, 15, and 19-36* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10, 13, and 16-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5, & 16*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I Claims 1-18, drawn to a method of accelerating the rate of mucociliary clearance, classified in Class 514, subclass 2.

Group II Claims 19-36, drawn to using Kunitz-type serine protease inhibitor of manufacturing a medicament for accelerating the rate of mucociliary clearance using , classification is unknown because the claim is drawn to non-statutory method, i. e., general use.

Claims 1-10, 16-29 and 33-36 of are generic to a plurality of disclosed patentably distinct species comprising Kunitz-type serine protease inhibitor. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case, the different invention are independent method having different steps, effects and products.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Emily Miao on September 10, 2002 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-18. Also, she elected the species of SEQ ID NO: 52 with traverse.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Claims 1-10, 13, and 16-18 are under consideration as they pertain to SEQ ID NO: 52.

This application has been filed apparently with informal drawings which are acceptable for examination purposes only. The drawings are not numbered in most cases. Figure 4C is not numbered properly. Each page of Figure 4C should be numbered Figure 4C, 4D, 4E ..... *etc.* Also, currently numbered Figures 4D, 4E ...*etc.* should be renumbered subsequently. Applicant should amend the Figure description and the specification to reflect the changes in renumbering the Figures. Formal drawings are required.

The use of the trademark names has been noted in this application, see for example pages 64 and 65. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) the following reason: Through out the specification, there are many reference to bikunin(7-64), bikunin(1-170), and bikunin(102-159), see for example page 20, lines 18 and 19, page 23, line 11, page 33, line 36, page 34, lines 10 and 27, and line 37, lines 2 and 3, which are not fragments are not identified by sequence identification number as required. Applicants are required to comply with the sequence rules.

Since the sequence listing is part of the disclosure, identifying the amino acid sequence by a sequence identification number in the claims is sufficient description of the

amino acid sequence. Applicants are advised to remove the amino acid sequences from the claims to eliminate a potential source of typographical errors in the claims.

The disclosure is objected to because of the following informalities: The specification contains the undefined abbreviation "AMC" on page 34, lines 1 and 2. Abbreviation must be defined at lease once in the specification.
Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 13, and 16-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases "subject in need of such a treatment" in claim 1, and "physiologically buffered solution" in claim 10 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, the phrases "subject in need of such a treatment" is assumed to mean "subject suffering from allergy, asthma or cystic fibrosis. The phrase "physiologically buffered solution" is ignored because no reasonable interpretation could be given to the phrase.

(b) the phrase "according to the amino acid sequence of native human placental bikunin" in claim 18 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes, the phrase is assumed to mean SEQ ID NO: 1.

(c) claims 2-9, 16 and 17 are included in these rejections because they are dependent on a rejected claim and do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Rasche *et al.* [IDS, paper number 16, reference number 7, *Medizinische Klinik*, 72 (5), 145-160 (1975)].

Rasche *et al.* teach the use of aprotonin, a Kunitz-type serine protease, isolated from bovine organs and formulated in a commercially available pharmaceutical composition known as TRASYLOL® in the treatment of chronic obstructive bronchitis. TRASYLOL® inhibits the symptoms of the disease and is well tolerated by patents (claims 1 and 10), see English summery on page 116, right column. Also, they teach the administration of aprotinin by inhalation to the lungs (claims 2-4). Claims 5-9 are included in this rejection because the formulation of TRASYLOL® is not described in the article, and the examiner could not ascertains many of the details of experiments in the article because it is written in German.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 3-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Rasche *et al.* [IDS, paper number 16, reference number 7, *Medizinische Klinik*, 72 (5), 145-160 (1975)] in view of the state of the art.

The teaching of Rasche *et al.* as understood by the examiner is summarized above. Rasche *et al.* is a German language article, and the examiner is not sure of the details of the teaching of the article.

Rasche *et al.* provide one of ordinary skill in the art with motivation of using aprotinin composition for the treatments of lung conditions characterized by improper mucociliary clearance such as in the case of chronic obstructive bronchitis. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to formulate aprotinin in a composition appropriate for administration to human lungs. One of ordinary skill in the art would have been able to prepared several aersolizable compositions such as dry powder, suspensions, or solutions of aprotinin and use them for the treatment of indicated conditions by the administration of the composition directly to the lungs air ways. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

Claims 13, and 16-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Delaria *et al.* (J. Biol. Chem. 1997, 272 (18), 12209-12214) in view of the state of the art as exemplified by Rasche *et al.* [IDS, paper number 16, reference number 7, *Medizinische Klinik*, 72 (5), 145-160 (1975)], Fritz *et al.* (U. S. Patent 5,407,915), and O'Riordan *et al.* (IDS: Am. J. Respir. Crit. Care Med Vol. 155, pp. 1522-1528).

Delaria *et al.* teach the expression in SF9 cells and characterization of a soluble placental bikunin, having N-terminus sequence ADRER- and 170 amino acid residues corresponding to SEQ ID NO: 52 of the instant application, see the abstract and page 12211, the first two paragraph of the result section. Also, they teach the 170 amino acid residue protein contains two Kunitz-type domain corresponding to residues 7-64 and 102-159. Table 1 on page 12213 shows the inhibition constants for bikunin of SEQ ID NO: 52, two polypeptide corresponding to the two Kunitz domain of bikunin, and aprotinin inhibition

of various serine proteases. The results indicates that bikunin and its Kunitz fragments are potent inhibitors of serine proteases. It should be noted that bikunin1-170 is expressed in SF9 insect cells, and therefor is expected to be glycosylated. Delaria *et al.* do not teach the use of bikunin1-170 in the treatment of any diseases or conditions.

The teachings of Rasche *et al.* are summarized above.

Fritz *et al.* teach the desirability of low molecular weight human protein having a Kunitz-type domain for the treatment of diseases related to excess activity of neutrophil elastase such as emphysema, shock lung and ARDS, see column 1, lines 24-62. They teach a human inter-α-trypsin inhibitor ITI (bikunin) that differs from the bikunin of the instant application. Said inhibitor contains two Kunitz domain corresponding to residues 22-77 and 78-147 each of which is capable of inhibiting serine proteases, see the paragraph bridging column 1 and 2. Also, they teach various analogs of bikunin and its Kunitz domains that are specific inhibitors, see examples 1-5, and the formulation of the inhibitors into pharmaceutical compositions, see from column 4, line 37 through column 6, line 48, in particular column 5, lines 40-46.

O'Riordan *et al.* teach that antigen-induced bronco constriction is associated with impairment of mucociliary clearance, and the contribution of neutrophil elastase to the development to the development of such a condition.

Rasche *et al.* provide one of ordinary skill in the art with motivation and expectation of success to develop a method for treatment of a of lung conditions characterized by improper mucociliary clearance such as in the case of chronic obstructive bronchitis using composition of Kunitz-type inhibitor. Fritz *et al.* motivate one of ordinary skill in the art to use human proteins having low molecular weigh such as bikunin. Delaria *et al.* provide one of ordinary skill in the art with motivation to use the placental bikunin expressed in mammalian cells in the pharmaceutical composition as they teach a water soluble glycosylated human bikunin. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to formulate the glycosylated human protein of SEQ ID NO: 52 taught by Delaria *et al.* in a pharmaceutical composition by well known methods in the art such as those taught by Fritz *et al.* and use the composition in a method to treat a condition related to the impairment of mucociliary clearance similar to that taught by Rasche *et al.* (claim 13, and 16). It should be noted that one of ordinary skill in the art would have been able to prepared several aersolizable compositions such as dry powder, suspensions, or solutions of SEQ ID NO: 52 and use them for the treatment of indicated conditions by the administration of the composition directly to the lungs air ways. Also, it should be noted all the cystine residues cited in claim 18 are found in SEQ ID NO: 52, and therefore, the protein is expected to form the requisite disulfide bonds (claims 17 and 18).

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 13, and 16-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 15-18 of copending Application No. 09/441,966 (966). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-10 of the instant application a generic claims drawn to the a method of accelerating the rate of mucociliary clearance comprising administering a composition comprising Kunitz-type serine protease inhibitor. Also, claim 13 from which claims 16-18 are dependent are limited to a specific Kunitz-type serine protease inhibitor identified by amino acid sequences. Claims 1-10 and 15-18 of the '966 application are drawn to the same method. The claims of the 966 application are narrower in scope because the broadest claim define amino acid sequences. Claim 1 of the 966 application contain SEQ ID NO: 52 which is the elected species for prosecution in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is

(703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner